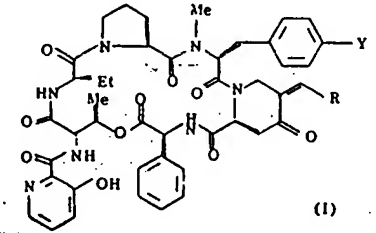
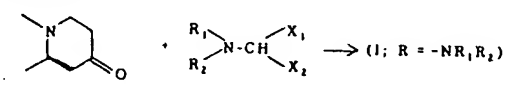


EP 0 133 098 - 02

Filed in 327A EP 0 133 098

(in french)

<p>85-039663/07 B02 RHONE-POULENC SANTE 13.07.83-FR-011706 (13.02.85) C07k-07 New 5-delta-methylene substd. synergistin derivs. - useful as intermediates for antibacterials</p>	<p>RHON 13.07.83 *EP -133-098-A B(2-P1, 2-S) 2 0 9 0</p>
<p>C85-017007 D/S: AT BE CH DE FR GB IT LI LU NL SE. Synergistin derivs. of formula (I), their addn. salts with acids and N-bases, metal salts and (where appropriate) their isomers or mixts. are new:</p>  <p>(I)</p>	<p>Y = H or Me<sub>2</sub>N; R = (a) H or OH; (b) NR<sub>1</sub>R<sub>2</sub> or (c) halo, trimethylsilyloxy, dialkylphosphoryloxy, -OSO<sub>2</sub>R<sub>3</sub> or -OCOR<sub>4</sub>; R<sub>1</sub> and R<sub>2</sub> = H, phenyl or pyridyl (opt. substd. by di(1-4C)-alkylamino), 1-10C alkyl (opt. substd. by OH, SH, COOH, pyridyl, anilino, alkylamino or dialkylamino (with at least one alkyl substd. by OH, SH, COOH or anilino)), 3-4C alkenyl or alkynyl; or R<sub>1</sub> and R<sub>2</sub> together complete a 5- or 6-membered heterocycle opt. contg. another O, S or N (opt. alkyl substd.) atom; R<sub>3</sub> = alkyl, CF<sub>3</sub>, CCl<sub>3</sub> or phenyl (opt. substd. by halo, alkyl or NO<sub>2</sub>); R<sub>4</sub> = as R<sub>3</sub> or also alkylcarbonylmethyl, 2-(alkylcarbonyl)-ethyl, alkoxycarbonylmethyl, 2-(alkoxycarbonyl)ethyl or alkoxy; all alkyl contain 1-4C. <b>MORE SPECIFICALLY</b> R = H, OH or NR<sub>1</sub>R<sub>2</sub>; R<sub>1</sub>' and R<sub>2</sub>' = H, phenyl (opt. substd. by dialkylamino), EP-133098-A.</p>

<p>alkyl (opt. substd. by OH, SH, COOH, pyridyl, anilino, alkylamino or dialkylamino, with alkyl substd. by OH) or 3-4C alkynyl.</p> <p><b>USE</b> (I) are intermediates in the synthesis of water-soluble antibacterial synergistin derivs. (which are claimed in EP-133097).</p> <p><b>PREPARATION</b></p>  <p>R<sub>1</sub> and R<sub>2</sub> = 1-4C alkyl or together complete a heterocycle; X<sub>1</sub> and X<sub>2</sub> = alkoxy or substd. amino as defined above for NR<sub>1</sub>R<sub>2</sub>.</p> <p>Reaction is pref. at around 20°C, esp. using tert. butoxy bis(dimethylamino)methane (II) as reactant. The prod. can be reacted (1) with an alkali borohydride in the presence of a strong organic acid to give (I; R = H); (2) with another amine to exchange the NR<sub>1</sub>R<sub>2</sub> gp.; (3) hydrolysed to give R = OH which is then reacted</p>	<p>with halogenating agent, R'-halo. (R' = trimethylsilyloxy, dialkylphosphoryloxy, OSO<sub>2</sub>R<sub>3</sub> or OCOR<sub>4</sub>).</p> <p><b>EXAMPLE</b> A soln. of 46g. pristnamycin 1A in 460 cc. 1,2-dichloroethane was treated with 230 cc. (II) and the mixt. stirred for 18 hr. at 20°C. It was then diluted with 1 l. dichloromethane, washed 3 times with 0.4% aq. NH<sub>4</sub>Cl, dried and concd. The residue was triturated with 600cc. water, filtered and the filtrate concd. to dryness to give 41g. crude 5δ-dimethylaminomethylene pristnamycin 1A. A 23.5g. sample of this was chromatographed to give 12g. pure material of m.pt. about 195°C. (76pp1251HDDwgNo0/0). (F) ISR: US4355112 5.Jnl. Ref.</p> <p>EP-133098-A</p>
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(54) Nouveaux dérivés de synergistines et leur préparation.

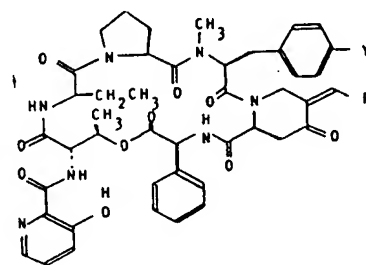
(57) Nouveaux dérivés de synergistines de formule (I) dans laquelle Y = H ou N(CH<sub>3</sub>)<sub>2</sub> et R représente

a) soit H ou OH

b) soit un radical de formule NR<sub>1</sub>R<sub>2</sub> dans laquelle R<sub>1</sub> et R<sub>2</sub> = H, phényle, pyridyle (éventuellement substitués par dialcylamino (1 à 4 C) ou alcoyle (1 à 10 C) (éventuellement substitué par OH, SH, COOH, anilino, alcoylamino ou dialcylamino dont au moins l'une des parties alcoyle est substituée par OH, SH, COOH ou anilino) ou alcényle (3 ou 4 C), alcynyle (3 ou 4 C) ou bien R<sub>1</sub> et R<sub>2</sub> forment ensemble un hétérocycle contenant éventuellement un autre hétéroatome tel que O, S ou N (éventuellement substitué par alcoyle).

c) soit un atome d'halogène, un radical triméthylsilyloxy, dialcylphosphoryloxy ou un radical -OSO<sub>2</sub>R<sub>3</sub> ou -OCOR<sub>4</sub>, R<sub>3</sub> étant alcoyle, trifluorométhyle, trichlorométhyle, phényle éventuellement substitué et R<sub>4</sub> étant défini comme R<sub>1</sub> ou un radical acylalcoyle, alcoxycarbonylalcoyle ou alcoyloxy, ainsi que leurs sels et leur préparation.

Ces produits sont utiles comme intermédiaires de synthèse.



(1)